Border Zones of Evidence: How Non-evidence Based Factors Influence Evidence Generation and Clinical Practice in Stroke Medicine

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View Point

Border Zones of Evidence: How Non-evidence Based Factors Influence Evidence Generation and Clinical Practice in Stroke Medicine

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Abstract

The interpretation of the results of clinical trials should be done by examining the finer prints of extraneous factors such as stopping rules, interim analysis, intricacies of patient selection, and the rationale of decisions that lead to non-prespecified termination. This can be done only by critical education in the art and science of interpretation of evidence emerging from clinical trials. The pioneering pivotal studies, namely, NINDS rtPA and ECASS III trials, hold disproportionate influence in determining the contours of the subsequent fate of clinical trials and treatment guidelines. It needs to be recognized that the pooling of studies using dissimilar trial designs, notwithstanding similar patient profiles, would undermine the positive signal emerging from the studies that have used better selection methodologies to homogenize the study population.

Keywords: Acute stroke trials, border zones of evidence, stroke medicine

Introduction

Clinical trials of endovascular intervention for emergent large vessel occlusion have revolutionized the management of acute ischemic stroke. This has been achieved after more than a decade of iteration of various clinical trial paradigms.

We had opined earlier that the design characteristics of the positive clinical trial may unduly influence the evolution of trial designs for settling unanswered questions, and delay the process of evidence generation.[1,2] This phenomenon may be a result of a too narrow interpretation of the data from clinical trials and in certain cases an outcome of a confluence of multiple extraneous factors not directly related to scientific evidence in question.

In this article, we present a few restrictions in practice imposed by excessive and undesirable extrapolation of evidence from clinical trials. In addition, we bring about the "blind-alleys" of evidence brought about by premature termination of certain clinical trials. We strive to elucidate the issues in the generation of meaningful evidence in the paradigm of evidence-based medicine when extraneous factors influence the conduct/conclusion of clinical studies.

Alteplase in Emergent Large Vessel Occlusion

The guideline for intravenous (IV) thrombolysis using alteplase has developed from the inclusion and exclusion criteria of the NINDS rtPA (National Institute of Neurological Diseases and Stroke- tissue plasminogen activator) trial published in 1995.[3] When the guidelines for IV thrombolysis evolved it was quite reasonable that NINDS rtPA trials eligibility criteria be followed as closely as possible,[4] as NINDS rPA trial was the sole positive trial of the dozen clinical trials that failed to show benefit for thrombolysis with alteplase in acute ischemic stroke.[5,6]

American Heart Association/American Stroke Association (AHA/ASA) guidelines state that alteplase has to be administered in any patient who presents with acute ischemic stroke within the therapeutic window satisfying the eligibility criteria[7] which largely represents the NINDS rtPA trial selection criteria. It further states that for the administration of alteplase there is no need for any imaging modality beyond non-contrast computed tomography (CT) scan. However, it is not possible to make a diagnosis of large vessel occlusion based on the selection criteria of NINDS rtPA or ECASS III trials; two trials that have shown results in favor of IV thrombolysis. The guidelines require CT angiography (CTA) for demonstration of large vessel occlusion. The clot lysis using alteplase is as low

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as 30%[8] in visible intracranial occlusion. If the clot length is beyond 5 mm the likelihood of clot lysis falls drastically and it is negligible if the clot length is more than 8 mm.[9] In many of the patients with large clot length and proximal thrombus, IV thrombolysis is not only ineffective but may be deleterious as the incomplete action of IV thrombolytic agent make the clot friable and prone to distal embolism that many times are not amenable to thrombectomy. It is a common clinical situation that while the proximal thrombus is removed and recanalization achieved, the distal thrombus would cause infarcts further causing clinical deficits, confounding the improvement effected by successful proximal thrombectomy.[10] The insistence of administration of alteplase immediately after non-contrast CT causes a scenario where ischemic stroke with large vessel occlusion due to large clot burden, get IV lytic agent that not only is ineffective but may be deleterious to the beneficial effects of the definitive treatment of thrombectomy. While many would demand a clinical trial to resolve this issue, we believe that in centers with good process standards and rapid recanalization rates, the decision to give IV thrombolysis before thrombectomy in proximal large vessel occlusion should be made case-by-case based on the review of CTA. In our view, considering direct mechanical thrombectomy in large vessel occlusion with a clot size >8 mm makes a strong case based on available evidence. The ongoing SWIFT-DIRECT would shed light on this issue.[11]

In many nations, the administration of alteplase is protocolized making it difficult for the physicians to make a judgment based on the local circumstances.

A scientifically reasonable guideline would be to allow the physician to go ahead with CTA and determine the future course of action incorporating the CTA findings. In most centers, a CTA can be done within a matter of 5–10 min. We view that insistence of guidelines to demand administration of alteplase before vascular imaging is an unreasonable imposition of incomplete evidence on the treatment autonomy of the physician. However, it is a reasonable policy for administering IV alteplase if CTA is not available or the patient has to be transferred to another center. Nevertheless, the best policy is to have CTA in the first setting when a patient is undergoing imaging. This would allow proper therapeutic planning and prognostication of the patient's outcome.

Antiplatelet agent after intravenous thrombolysis

In NINDS rtPA trial aspirin was avoided in the initial 24 h after thrombolysis. This stipulation is quite reasonable as most of the initial thrombolysis trials showed higher rates of intracerebral hemorrhage (ICH). However, after the publication of the NINDS rtPA trial, we have experiences of tens of thousands of patients who had undergone IV thrombolysis for ischemic stroke. In the SITS-MOST registry representing the real-life outcome of IV thrombolysis, the incidence of symptomatic intracerebral hemorrhage (SICH) is less than 2%. Studies have demonstrated that the incidence of ICH after IV thrombolysis in a patient on antiplatelet is not high.[12] However, in many practice settings, the guideline is applied rigorously that it conflicts with the requirements of practices that have evolved later. For instance, in endovascular intervention, there are situations where it may be needed to apply intracranial stents due to conditions like intracranial atherosclerosis. Although stenting in ELVO due to intracranial atherosclerosis has not been demonstrated as a practice in a controlled trial paradigm, the current practice of endovascular intervention many times entails such a scenario. The insistence of withholding antiplatelet until 24 h would potentially jeopardize the situation as the incidence of stent thrombosis is potentially higher than that of post thrombolysis ICH following antiplatelet use.

Although many practitioners would forgo the practice guidelines in favor of stenting and antiplatelet use, many countries where guidelines are protocolized, and various components of the treatment are administrated by different disciplines, it creates hurdles in the practice.

MELT and Urokinase

The almost "absolutist" interpretation of established evidence over an emerging practice is an undesirable phenomenon seen in the practice of evidence-based medicine. A similar practice was seen when the Middle Cerebral Artery Embolism Local Fibrinolytic Intervention Trial (MELT) was testing intraarterial (IA) urokinase in Japan between 2002 and 2005.[13] Japanese investigators had used an opportunity window available in Japan as IV tPA was in the process of regulatory clearance. However, as the tPA got regulatory clearance, the study was terminated despite early trends favoring IA urokinase. A meta-analysis combining halfway terminated MELT and Prolyse in Acute Cerebral Thromboembolism (PROACT) trials had shown benefit in favor of IA urokinase.[14] However, the question was not pursued further as the relevant agencies were not interested. In this instance, "would-be" evidence is suppressed by "emerged" evidence by citing regulatory requirements. We consider such an interpretation of established evidence as a hindrance to the free evolution of scientific evidence in medicine.

We propose that in such scenarios the "effect size" of the "emerged evidence" should be compared against the possible "effect size" of the "emerging evidence." For instance, the effect size of IV tPA is 13% with a number needed to treat of 8 while the effect size of PROACT II from earlier studies was 15% with an number needed to treat of 6. The premature termination of an endovascular trial like MELT sidestepped a whole treatment paradigm and delayed the evolution of scientific evidence in favor of endovascular treatment by decades.

WAKE-UP trial and EXTEND trial

The efficacy and safety of MRI-based thrombolysis in Wake-Up stroke (WAKE-UP) and extending the time for thrombolysis in emergency neurological deficits (EXTEND) trials are two interesting addition to the literature extending the indications of thrombolysis beyond the traditional therapeutic window limits dictated by the time of onset of stroke.[15,16] WAKE-UP trial

studied selection of wake up ischemic stroke patients for IV thrombolysis based on DWI-FLAIR mismatch while EXTEND studied selection of ischemic stroke for IV thrombolysis based on automated perfusion imaging. Both trials were prematurely terminated. WAKE-UP trial was terminated as the funding got exhausted, while the EXTEND trial was stopped as the data and safety monitoring board (DSMB) thought that with the publication of positive WAKE-UP trial the EXTEND trial has lost clinical equipoise. WAKE-UP trial showed that the treatment arm is significantly better than the control in the primary outcome parameters, but most of the secondary outcomes were not significantly different after correction for multiple comparisons. For the primary outcome parameter of favorable clinical outcome of 0 or 1 on the modified Rankin scale (mRS) at 90 days the absolute difference between the arms was 11.5, giving a number needed to treat 9. In the EXTEND trial, the benefit was only shown in the primary outcome of mRS at 90 days (an absolute difference of 5.9). All the secondary outcomes of the study were neutral between the treatment and the control arms. The effect size of the EXTEND trial for the primary outcome was 5.9, giving a number needed to treat of 17.

The decision of DSMB to suggest termination of the EXTEND trial based on the results of the WAKE-UP trial seems surprising, as the studies represented different sets of questions. In the WAKE-UP trial, the use of an MRI DWI-FLAIR mismatch was intended to date the duration of onset of stroke. DWI-FLAIR mismatch is considered to predict the onset of stroke to less than 4.5 h with a moderate positive predictive value and a low negative predictive value. In the EXTEND trial, however, the perfusion defect used to determine the tissue viability and was considered the critical factor for enrolment.[16] Thus, while WAKE-UP trial used the NINDS-ECASS III paradigm, EXTEND used the extended window of therapeutic opportunity determined by perfusion defect. In other words, the WAKE-UP trial and EXTEND trial studied different paradigms. Results of the WAKE-UP trial do not affect clinical equipoise of the EXTEND trial. Interestingly, the authors of the EXTEND trial recommends another clinical trial to clarify the indecisive results of the study.

It appears that the idea of absence of clinical equipoise that made the DSMB to prematurely stop EXTEND neither existed before nor after the publication of the EXTEND. Thus, even after the publication of WAKE-UP and EXTEND trials the question thrombolysis in the wake-up stroke or the extended period after the onset of stroke is still uncertain. The results of prematurely terminated EXTEND only add to the uncertainty of the evidence in the area.

The impression of loss of equipoise EXTEND after the publication of the WAKE-UP trial is neither evidence-based nor theory-based. It is important to note that the consequence of "blind-alleys" of evidence left as a consequence of prematurely terminated large clinical studies be critically and empirically examined.

Tenecteplase for IV thrombolysis

Tenecteplase (TNK) is a third-generation plasminogen activator, with higher fibrin specificity and binding affinity to PAI-1. It has a 4-fold prolonged plasma half-life and can be administered as a single bolus. It is widely used for thrombolysis in myocardial infarction. Of the five trials published on TNK in acute ischemic stroke, the primary outcomes were in favor of TNK in two trials while the outcome was neutral for the remaining three trials.[17-22] Three of the neutral trials used the NINDS-rtPA trial paradigm of selecting patients solely using plain CT head. The two trials that showed benefit in favor of TNK used CT perfusion studies to select patients. A pooled analysis of the Australian-TNK trial and the subset of ATTEST (Alteplase-Teneecteplase Trial Evaluation for Stroke Thrombolysis) trial patients selected based on CT perfusion mismatch target showed that the tenecteplase arm has a better clinical outcome than the alteplase arm.[23] We would argue that ATTEST, NOR-TEST (Tenecteplase versus alteplase for management of acute ischemic stroke), Australian-TNK, and EXTEND-IA TNK (Tenecteplase versus Alteplase before Endovascular Therapy for Ischemic Stroke) trials are paradigmatically different studies and should not be analyzed together. In the EXTEND-IA TNK trial, the effect size of better recanalization of large arteries is significant enough for tenecteplase to prove as a better agent for bridging thrombolysis before endovascular intervention (22% for tenecteplase versus 10% for alteplase).[21] The authors in the latter study were prudent in choosing the recanalization rate as the primary outcome as the effect of thrombectomy that followed thrombolysis would have obscured the clinical difference of recanalization. This is particularly so as the recanalization with thrombolysis in large vessel occlusion is achieved in less than 10–20% of the patients and the number needed to show a difference would be quite large. The exact difference in the functional clinical outcome between tenecteplase and alteplase in patients selected for thrombolysis based on perfusion studies would be evident with the results of ongoing TASTE (Tenecteplase versus alteplase for stroke thrombolysis evaluation) trial.[24]

Conclusion

To conclude, we argue that interpretation of the results of clinical trials should be done looking into the finer prints of extraneous factors such as stopping rules, interim analysis, intricacies of patient selection, and the rationale of decisions that lead to non-prespecified termination. This can be done only by critical education in the art and science of interpretation of evidence emerging from clinical trials. The pioneering pivotal studies, such as NINDS rtPA and ECASS III trials, hold disproportionate influence in determining the contours of the subsequent fate of clinical trials and treatment guidelines. It needs to be recognized that the pooling of studies using dissimilar trial designs, notwithstanding similar patient profiles, would undermine the positive signal emerging from the studies that have used better selection methodologies to homogenize the study population.

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There are no conflicts of interest.

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